REMARKS

Applicant respectfully requests reconsideration of the present application in view of the foregoing amendments and in view of the reasons that follow.

Claim 14 is requested to be cancelled.

Claims 3, 4, 13, 20, 44-48 and 50 are currently being amended.

This amendment amends and/or deletes claims in this application. A detailed listing of all claims that are, or were, in the application, irrespective of whether the claim(s) remain under examination in the application, is presented, with an appropriate defined status identifier.

After amending the claims as set forth above, claims 1-5, 8-13, 15-31, 33-35, 38 and 44-57 are now pending in this application.

The Examiner states in the Advisory Action dated May 22, 2003 that the response after final that was filed on May 15, 2003 overcame the rejection under 35 U.S.C. § 112, first paragraph of claims 14, 44-48 and 50, the rejections under 35 U.S.C. § 112, second paragraph and all of the rejections under 35 U.S.C. § 102 and 103. Applicants thank the Examiner for withdrawing these rejections. Further, the Examiner states that he entered the amendment after final because it reduced issues for Appeal but that this response did not place the application in condition for allowance. The Examiner states that claims 1-5, 8-31, 33-35 38 and 44-57 are rejected and provides the following bases for maintaining the remaining two rejections:

Claims 13, 14, 44-48 and 50

Claims 13, 14, 44-48 and 50 remain rejected for an allegedly inadequate written description. In this regard, applicants previously provided two publications by Stripp and McGraw with the amendment after final as further cumulative evidence that mammalian cell specific promoters, such as epithelial cell specific promoters, were known and used by skilled artisans prior to or at the time of filing the present invention. However, the Examiner would

not consider these two publications, even though the amendment after final was entered. Applicants request that these two publications now be considered by the Examiner as further evidence of epithelial cell specific promoters along with the evidence that has been previously presented to show that many epithelial cell specific promoters are known and used by skilled artisans. Applicants have not resubmitted these publications with this response. Therefore, applicants again respectfully traverse this rejection and applicants request that the Examiner consider all of the publications previously submitted, along with the specification of the present application, particularly page 25, which recites

> The β_2AR promoter may be modified to include an epithelium-specific expression cassette.[21] This cassette includes regulatory elements from the human cytokeratin gene. It has been used to efficiently express reporter genes as well as the human cystic fibrosis transmembrane conductance regulatory protein (CFTR) in airway epithelial cells.[21] Other useful promoters that drive β_2AR expression are the human surfactant protein C promoter or the CC10 promoter. These promoters have been used to drive β_2AR gene expression in the airways of transgenic mice.[89] Any human promoter effective in the rat-derived SPOC1 cell line is useful in the present invention.

Applicants believe that they have provided sufficient information through the use of scientific publications that were available to skilled persons in the art to support the subgenus of mammalian cell specific promoters, and more specifically epithelial cell specific promoters and smooth muscle cell specific promoters. These publication provide a representative number of epithelial cell specific promoters that were available prior to and at the time of filing the provisional patent application upon which the present application claims priority.

To reiterate, the previous information provided to the Examiner includes previously submitted Exhibits 1 and 2, which disclose an epithelial cell specific promoter, human cytokeratin 18 (K18), and disclose how to prepare constructs containing this promoter for the epithelial-specific expression of a transgene in the airway epithelia. Further, previously submitted Exhibits 3 and 4 show that the human surfactant Protein B promoter, also an epithelial-specific promoter that as characterized by the Examiner is only active in distal alveolar epithelium (type II cells), and also see, Exhibit 3, page 5, 1st col., lines 4-5, and

bronchial tracheal epithelium (Clara cells). These two cell type are epithelial cells. Skilled persons in the art would know that these cells were epithelial cells.

The two publications, that applicants are requesting consideration of, one by Stripp *et al.*, *J.Biol. Chem.* 267:14703, published in 1992, identifying the promoter of the CC_{10} gene, a gene that is expressed in the epithelial cells, Clara cells, and a later publication by McGraw *et al.*, *Am.J. Physiol. Lung Cell Mol.Physiol.* 279: L379-L389 (2000) using the CC_{10} gene promoter described in Stripp *et al.* to limit expression of the β_2AR in Clara cells in transgenic mice provide further evidence that epithelial cell promoters were known and used by skilled persons.

In regard to the Examiner's concern that Clara cells may not be epithelial cells, Stripp *et al.* supports applicants' position that they are epithelial cells and the specification of the present application on pages 2 and 10 also support this assertion.

Although applicants submit that they have provided sufficient evidence to support the broader genus of mammalian cell specific promoters and more specifically, smooth muscle cell specific promoters, in an effort to expedite prosecution, applicants have amended or canceled claims that recite either of these groups of promoters. In this regard and as argued previously, the alpha actin promoter is mentioned on page 10, lines 22-24 of the present specification, as a promoter that was known and disclosed in McGraw *et al.* (1999), which was previously submitted as Exhibit 7. Previously submitted Exhibits 6 and 7 disclose the use of this promoter to express a transgene in the smooth muscle cells of transgenic mice and cell cultures, and therefore was recognized and used by persons skilled in the art..

Applicants submit that they have provided evidence that shows that epithelial cell specific promoters were known and available and methods of obtaining these promoters and inserting them into cassettes or vectors to express transgenes in cells in the airway were well known to persons skilled in the art prior to applicants invention.

As previously argued, the DNA sequences of many epithelial cell specific promoters have been described in many scientific publications, as evidenced by the publications cited in support of applicants' position in the present application which show that prior to and at the time of applicants invention, skilled persons could select, prepare and transfect airway cells and obtain expression of a transgene expressed under the control of these promoters. In view of the above information provided regarding what was known by persons skilled in the art, it

is submitted that the claimed invention is enabled, and it is requested that this rejection be withdrawn.

Claims 1-5, 8-38 and 44-50

Claims 1-5, 8-38 and 44-50 remain rejected as allegedly not enabled by the specification. Applicants respectfully traverse this rejection.

The Examiner states that applicants' previous response and Dr. Cornett's previous declaration are insufficient to overcome the rejection of claims. The Examiner states that the claims are allegedly not enabled because the evidence presented does not demonstrate that any β_2AR was expressed *in vivo*. The Examiner states that reporter gene studies are not predictive of therapeutic success, and that vector delivery is highly unpredictable.

Applicants herewith attach a second declaration by Dr. Cornett, in which he studied the impact on respiratory function and tissue expression of recombinant human β_2AR gene delivery to airway epithelia in a rat model. The data presented in Figures 1 and 2 of Dr. Cornett's second declaration dated October 16,2003, show that human β_2AR is expressed in the cells of rat lungs *in vivo* as evidenced by the decreased central airway resistance in treated animals as compared to untreated control animals, which is evidence of a therapeutic effect in rat lungs. Further, immunohistochemistry data shown in Figure 2 further support the expression of β_2AR in rat lungs *in vivo*.

Applicants respectfully request that the Examiner consider this further declaration by Dr. Cornett and accompanying figures supporting the expression of β2ARs in cells of the rat lung. In view of these arguments, it is requested that this rejection be withdrawn.

CONCLUSION

Applicant believes that the present application is now in condition for allowance. Favorable reconsideration of the application as amended is respectfully requested.

The Examiner is invited to contact the undersigned by telephone if it is felt that a telephone interview would advance the prosecution of the present application.

The Commissioner is hereby authorized to charge any additional fees which may be required regarding this application under 37 C.F.R. §§ 1.16-1.17, or credit any overpayment, to Deposit Account No. 19-0741. Should no proper payment be enclosed herewith, as by a check being in the wrong amount, unsigned, post-dated, otherwise improper or informal or even entirely missing, the Commissioner is authorized to charge the unpaid amount to Deposit Account No. 19-0741. If any extensions of time are needed for timely acceptance of papers submitted herewith, Applicant hereby petitions for such extension under 37 C.F.R. §1.136 and authorizes payment of any such extensions fees to Deposit Account No. 19-0741.

Respectfully submitted,

Date Oct 16, 2003

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